

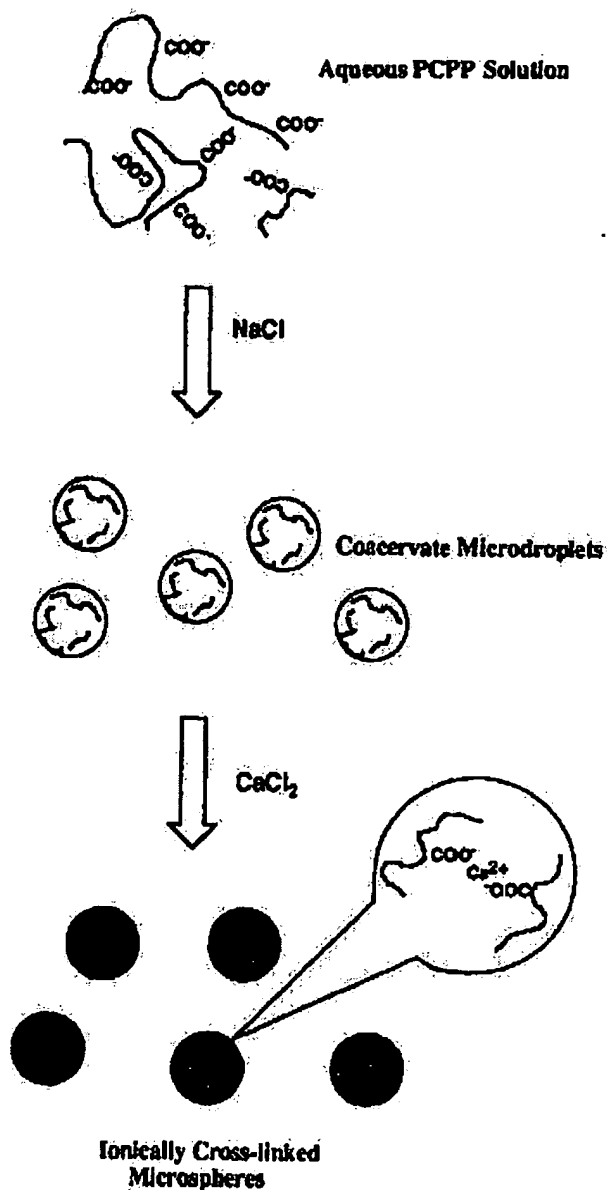
### REMARKS

All of the claims (1-7) stand rejected as being obvious under 35 U.S.C. § 103(a) over Andrianov *et al.*, [*Preparation of hydrogel microspheres by coacervation of aqueous polyphosphazene solutions*, Biomaterials 19 (1998) 109-115](hereinafter "Andrianov") in view of Pelta *et al.*, (*DNA Aggregation Induced by Polyamines and Cobalthexamine*, The Journal of Biological Chemistry, Vol. 271, No. 10, Issue of March 8, pp. 5656-5662, 1996)(hereinafter "Pelta"). Claims 1 and 2 are currently amended. The rejections are traversed below.

I. **The primary reference, Andrianov, teaches a two-step process for forming polyphosphazene microspheres, using inorganic reagents.**

Contrary to the Examiner's contention, Applicants have not argued that: "Andrianov does not teach the production of polyphosphazene microspheres, rather Andrianov teaches the production of polyphosphazene microdroplets." (Office Action, page 3). Applicants have argued the fact that Andrianov teaches a two-step process for preparing polyphosphazene hydrogel microspheres, consisting of: (1) the formation of microdroplets through the treatment of PCPP with sodium chloride (NaCl) and (2) the conversion of the microdroplets through ionic crosslinking to microspheres by *subsequent* treatment of the microdroplets with calcium chloride (CaCl<sub>2</sub>). Indeed, Andrianov states and illustrates the two-step process plainly:

"...In this study, we showed that PCPP microdroplets formed by sodium chloride induced coacervation can also be stabilized by simple addition of calcium chloride solutions to a coacervate system to form hydrogel microspheres (Scheme 1.)..." (Andrianov, page 111; Applicants' emphasis added).



Scheme 1.

(Andrianov, Scheme 1, page 112)

In contrast to Andrianov the amended claim is directed to a *single-step* process for forming polyphosphazene microspheres using *organic* amines, such as *spermine*. The claim as amended notes the use of the organic amine as a crosslinking agent in the formation of the polyphosphazene microspheres. Andrianov does not teach the formation of polyphosphazene

microspheres utilizing a single *organic* amine reagent; Andrianov teaches the use of two separate *inorganic* reagents. Accordingly, the claimed invention does not "encompass the teaching provided by Andrianov." (Office Action page 3).

Additionally, as Applicants have earlier argued, Andrianov makes no mention of *organic amines* in general, or of *spermine* in particular. In fact, on the use of poly[di(carboxylatophenoxy)phosphazene] for microencapsulation, Andrianov teaches away from the use of organic solvents altogether:

"The ability of poly[di(carboxylatophenoxy)phosphazene], PCPP (1) to form an ionotropic gel in the presence of calcium ions under mild physiological conditions and **without need of organic solvents** or elevated temperatures makes it an attractive candidate as a material for microencapsulation [4-6]." (See Andrianov, page 109, last ¶, first column)(Applicants' emphasis added).

In response to *this* argument the Examiner contends that Andrianov *does* use organic solvents with PCPP, and that the organic solvent used by Andrianov is *sodium chloride*. [???] Upon closer reflection the Examiner will surely appreciate that sodium chloride does not contain any carbon atoms, and therefore it is **not** an "organic" solvent.

Accordingly, nothing in Andrianov would suggest that polyphosphazene microspheres could be formed by using an *organic* amine as **both** a coacervating agent and as a crosslinking agent. Much less would Andrianov suggest using an *organic amine* in a *one-step* process to produce polyphosphazene microspheres, instead of Andrianov's *two-step* process involving *sodium chloride* followed by *calcium chloride*.

## II. **Nothing in the secondary reference, Pelta, cures the deficiencies of Andrianov.**

The secondary reference, Pelta, teaches the use of polyamines, such as spermine, to precipitate DNA molecules. Pelta makes no mention of *polyphosphazenes* or of *microspheres*.

Nothing in Pelta indicates or suggests that his use of spermine to precipitate DNA ultimately results in the formation of *DNA microspheres*, ergo much less could Pelta suggest that the use of spermine with a polyphosphazene would ultimately result in the formation of *polyphosphazene microspheres*.

Yet, the Examiner argues that it would have been prima facie obvious for one of ordinary skill to substitute Pelta's spermine for Andrianov's sodium chloride, insofar as they are both art recognized coacervating agents, and therefore "functional equivalent[s]." However, even if Pelta's spermine *was* the functional equivalent of Andrianov's sodium chloride, which (for the reasons explained below) it is **not**, the *functional equivalency* of a claim *as a whole* is not the test for obviousness, and much less is the *functional equivalency* of a *single claim element* found in the prior art the appropriate test for obviousness. The late Judge Rich explained it succinctly over forty years ago:

"The defect which we find in the reasoning employed below to support the rejection here is not only that it ignores the express provision of the statute as stated is section 103 but that it also ignores the fact that **it is advantageous to the public in the promotion of progress of the useful arts, the Constitutional objective of the patent law, to provide inducement for the invention of devices which are the functional equivalents of devices already known.** It is not the object of the policy behind the patent system to encourage satisfaction with or commercialization only of the first device for performing a given function that happens to come along. And for those who may be interested in promoting competition in the interest of the consuming public, **the greater the number of functionally equivalent devices which are encouraged onto the market by patent protection, the better off the consumer will be. Therefore the test is obviousness of the invention and not whether it serves the same purpose as previous inventions.**" *Application of Flint*, 51 C.C.P.A. 1230, 1235-36 (CCPA 1964)(Applicant's emphasis added).

Judge Rich's admonishment could not have greater relevance than to the vaccine formulation arts, wherein the variation of consumer choice is a function of the obsolescences dictated by each successive cold and flu season, or by each successive disease mutation. Clearly, whatever

"functional equivalency" spermine may have with sodium chloride as a *coacervating agent*, that "functional equivalency" does not render obvious the *claimed* combination of making polyphosphazene microspheres in a *one-step / organic amine-utilizing* process.

As taught by Andrianov the preparation of polyphosphazene hydrogel microspheres generally requires a separate *crosslinking* agent providing multivalent cations (Andrianov Scheme 1, e.g.,  $\text{Ca}^{+2}$ ). The art-accepted necessity of an ionic crosslinking agent for microsphere formation is confirmed by further polyphosphazene hydrogel references:

#### "Polymers for Formation of Hydrogels

Other polymeric materials that may be useful include hydrogels such as the naturally occurring polysaccharides like alginate, as well as synthetic hydrogel materials such as some of the polyacrylic acids, **polyphosphazenes**, polyethylene glycol-PLGA copolymers and other synthetic biodegradable polymers which absorb up to 90% of the final weight of water.

The polymeric material which is mixed with GM-CSF for implantation into the body should form a hydrogel. A hydrogel is defined as a substance formed when an organic polymer (natural or synthetic) is cross-linked via covalent, ionic, or hydrogen bonds to create a three-dimensional open-lattice structure which entraps water molecules to form a gel. Examples of materials which can be used to form a hydrogel include polysaccharides such as alginate, **polyphosphazenes, and polyacrylates, which are crosslinked ionically**, or block copolymers such as Pluronics<sup>TM</sup> or Tetronics<sup>TM</sup>, polyethylene oxide-polypropylene glycol block copolymers which are crosslinked by temperature or pH, respectively. Other materials include proteins such as fibrin, polymers such as polyvinylpyrrolidone, hyaluronic acid and collagen. U.S. Pat. Nos. 5,286,495 and 5,410,016 to Hubbell, et al., describe useful materials for forming biocompatible hydrogels." (See col. 5, lines 34-59 of U.S. Patent 5,942,253 issued August 24, 1999 to Gombotz *et al.*; "hereinafter Gombotz"; attached hereto as **Exhibit D**; Applicants' emphasis added).

**"Microspheres**, or solid microparticles, can be prepared using any of a number of techniques known to those skilled in the art. GM-CSF appears to be unusually stable to processing, especially in the presence of organic solvents, which facilitates microparticle formation containing GM-CSF having very high levels of bioactivity, typically greater than 90% as compared to the GM-CSF prior to incorporation into the microparticles. Examples of methods for preparation include solvent evaporation, spray drying, solvent extraction and other methods known to those skilled in the art. **As discussed above, hydrogels are typically formed by ionic crosslinking, by addition of ions or polyions, or**

**photocrosslinking or other forms of chemical crosslinking.**" (See Gombotz col. 7, lines 31-45; Applicants' emphasis added).

There is nothing in either of the Examiner-cited references that teaches or suggests that polyphosphazene microspheres can be made *without* such a crosslinking agent, and therefore under the Examiner's *functional equivalence* logic the Andrianov-educated and Pelta-educated artisan endeavoring to make polyphosphazene microspheres would consider it necessary to find both a coacervating agent and a crosslinking agent, or a single agent capable of both coacervating and crosslinking in a *dual* capacity. The artisan would *only* find the latter such teaching in the instant specification (through impermissible hindsight), wherein it is explained that the organic amine plays the *dual* role of both *coacervating agent and crosslinking agent*:

"A further advantage of the amine coacervate method over the prior art is that it is essentially a single step process. **As the coacervation agent, the amine initiates microdroplet formation** through electrostatic screening that decreases the polymer's solubility and causes the polymer to collapse. **As the cross-linking agent, the amine decreases the polymer's chain mobility and thereby arrests the growth of the microdroplet at the desired size.**" (Second Substitute Specification, pages 3-4; Applicants' emphasis added).

While Pelta may teach that spermine is a coacervating agent, with regard to its ability to aggregate *DNA molecules*, there is nothing in Pelta that commends spermine as having *crosslinking* properties such as could form *polyphosphazene microspheres*. Indeed, Pelta doesn't even mention the term *crosslinking*.

Moreover, the primacy that the Examiner ascribes to spermine and sodium chloride being *coacervating agents* as a makeweight for motivation is ill-founded, since the mechanism of this process is not currently understood, and the term *coacervation* is only used for descriptive purposes in the specification. Nowhere in the claims is the process for microsphere production identified as being a "coacervation process." Although applicants *believe* that coacervation phenomenon can play a role in the described single step process, this role is not fully understood

in the art. Other terms, like "ionic complexation" have also been suggested for the description of the process. Indeed, the art's lack of fully understanding the phenomenon of coacervation is even discussed in Pelta itself, wherein a "coacervate" is only one of several suggested states proposed to describe polymer precipitation:

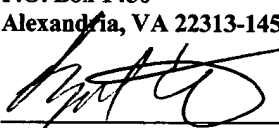
**"Bungenberg de Jong has described the precipitation of numerous polymers and colloids under various conditions (10). According to his nomenclature, the precipitate can be an ordered solid (a true crystal) or can be in an amorphous state, either solid (a flocculate) or liquid (a coacervate). He has specifically described the precipitation of numerous polyelectrolytes in presence of micro-ions or polyelectrolytes and introduced the term of complex coacervation to describe the phase separation occurring in such system. In our experiments, we observe such a phase separation, but the precipitate, instead of being amorphous, is a highly ordered fluid. Nevertheless we propose that it should be considered as a complex coacervate (as already done for polylysine-DNA complexes (22))."** We note here that the term "complex coacervation" is often specifically used to describe a complex between oppositely charged polyelectrolytes (23). However the original definition of Bungenberg de Jong encompasses the condensation of DNA by 3+ and 4+ cations (p. 336 in (10) )." (See Pelta page 5660, 1<sup>st</sup> col. 2<sup>nd</sup> full ¶; Applicants' emphasis added).

Applicants are not aware of *any* prior art that described the single step production of stable microspheres using *any* coacervating agents, and the Examiner argued position of substituting *any* coacervating agent for the purpose of producing polyphosphazene microspheres in a *single step* is clearly not obvious. Accordingly, *at the time the invention was made* the artisan having the guidance of Andrianov and Pelta, would **not** have *reasonably expected* that (1) the *substitution* of Pelta's spermine for Andrianov's NaCl and (2) the *elimination* of Andrianov's calcium chloride, would produce a polyphosphazene microsphere.

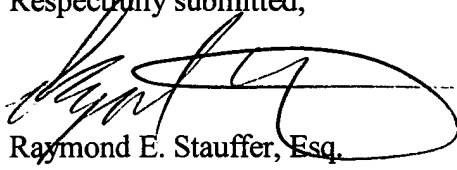
In view of the foregoing, Applicants submit that independent claim 1 is non-obvious over Andrianov in view of Pelta. The remaining claims, all of which depend from independent claim 1, are therefore similarly non-obvious over Andrianov in view of Pelta.

In further view of the foregoing, Applicants submit that the application is in condition for allowance, and they therefore request its prompt passage to issue.

It is believed that no further fees are due. However, if any further fee is due it should be charged to Deposit Account No.: 03-0678. Similarly, any credit for overpayment should be credited to Deposit Account No.: 03-0678.

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